REMARKS

Claims 22-33 and 49-92 are pending in the subject application. Claims 22 and 53 have been amended. The amendments to claims 22 and 53 are supported by the specification as filed (see, e.g. the originally filed claims and page 5, first paragraph), and no new matter is presented. Favorable reconsideration in light of the remarks which follow is respectfully requested.

Applicants further note that claim 65 has been "amended" herein to revert back to the claim as is was originally submitted. During prosecution (in Applicants' January 7, 2004 Response and Applicants' December 21, 2004 Response), a typographical error was made in which the range of claim 65 was entered as "about 80nm to about 100nm" rather than the originally submitted "about 50nm to about 200 nm". However, this was not made as an "amendment" nor was it indicated as an amendment. Rather, the claims were maintained but the ranges incorrectly entered due to a typographical error. Thus, applicants' have "amended" the range herein to reflect the proper range as required.

1. Double Patenting

U.S. Patent No. 6,165,500

Claims 53-91 are rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-35 of U.S. Patent No. 6,165,500 (US'500).

The Office asserts that "Instant claims are drawn to treatment of a mammal by administering the same transfersomes to the skin or mucous membrane of the mammal." Applicants respectfully disagree.

US'500 clearly describes a preparation, method of forming a preparation and use of a preparation that specifically has a solubilization point. In particular, the preparation is specifically formed such that the edge active substances is selected and added in a concentration which amounts to up to 99 mol-% of the concentration required for the induction of droplet solubilization (see Abstract). In fact, as set forth in US'500,

> [T]he conditions are determined under which the carrier vesicles are solubilized by the edge active substances. At this critical point the `vesicles` are maximally

> deformable owing to the fact that they are permanently formed and deformed. At the same time, however, they are also unstable and incapable of holding and transferring water soluble substances.
>
> Next, the carrier composition or concentration is adapted by reducing the edge activity in the system to an extent which ensures the vesicle stability as well vesicle deformability to be sufficiently high; this also ensures the permeation capacity of such carriers to be satisfactory. * * * The position of the corresponding optimum which one is looking for hereby depends on many boundary conditions. The type of agent molecules also plays an important role in this. The smaller and the more hydrophilic the agent to be transported, the further the carrier system must be spaced from the solubilization point; the desired shelf life of carriers is also important: upon approaching the solubilization point, the tendency of transfersomes to form larger particles may increase and the carrier's storage capacity simultaneously decrease.

Thus, the transfersomes of US'500 are based on a concept of an optimized approximation of the solubilization limit of the transfersomes. The concentration point of at least one of the amphiphilic components is determined wherein the vesicles become totally destabilized and solubilize. The concentration of this component is then adjusted to a concentration between 0.1 and 99% of that solubilization concentration.

The present transfersomes, on the other hand, do not have a solubilization point. Applicants unexpectedly discovered that certain components can be selected and combined such that no matter how much of the components is added, no solubilization occurs. This is an extremely advantageous discovery that eliminates time consuming and burdensome steps in forming the preparations and that provides improved preparations that are more stable than those presently available because they will not solubilize.

Thus, the transfersomes of the present invention clearly are not the same as those described by US'500. The present transfersomes have no solubilization point, while the transfersomes of US'500 have a solubilization point. Accordingly, US'500 does not teach or suggest a method for using applicants presently disclosed preparations.

Accordingly, claims 53-91 are patentable over US'500. Reconsideration and withdrawal of the rejection is respectfully requested.

U.S.S.N. 10/357,618

Claims 22-33 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting over claims 69-87 and 101-103 of U.S.S.N. 10/357,618 (USSN'618).

The Office asserts that the instant claims "are drawn to a method of preparation of same transfersomes" Applicants respectfully disagree.

USSN'618 clearly describes a composition, method of forming a composition and use of a composition that specifically has a solubilization point. As specifically set forth in USSN'618:

> [0026] All compositions according to the present invention comprising three amphipatic compounds which together form extended surface aggregates either have a defined solubilization point, or do comprise more than 0.1 mol % of the solubilizing amount of those components which at higher concentrations would solubilize the extended surface aggregates.

As discussed above, the present transfersomes do not have a solubilization point. Thus, the transfersomes of the present invention clearly are not the same as those described by USSN'618. The present transfersomes have no solubilization point, while the transfersomes of US'500 have a solubilization point. Accordingly, USSN'618 does not teach or suggest method for producing a preparation in accordance with applicants' claims, wherein the method involves the selection of first and second amphiphilic components and active ingredients such that, independently of the concentrations of the first and second amphiphilic components and the active ingredient, no solubilization of the vesicles in the suspension occurs.

Accordingly, claims 22-33 are patentable over USSN'618. Reconsideration and withdrawal of the rejection is respectfully requested.

2. 35 U.S.C. 102 Rejections

Claims 22-33 and 49-92 are rejected under 35 U.S.C. 102(b) over EP 0 475 160 (EP'160)(English equivalent US 6,165,500 "US'500). Applicants respectfully traverse for the same reasons as set forth above regarding US'500.

Applicants claim, in independent claim 22, a method for producing a preparation for transporting at least one active ingredient through the skin or mucous membrane of a mammal. A method for producing a preparation for transporting at least one active ingredient through the skin or mucous membrane of a mammal comprising: selecting a pharmaceutically acceptable suspending medium; selecting at least one active ingredient; selecting a first amphiphilic lipid component and a second amphiphilic component such that the solubility of the second amphiphilic component in the pharmaceutically acceptable suspending medium is at least ten times greater than the solubility of the first amphiphilic lipid component in the medium; producing a mixture of the pharmaceutically acceptable suspending medium, first amphiphilic lipid component, second amphiphilic component and at least one active ingredient; producing a vesicle suspension by means of applying energy to the mixture, the vesicles comprising liquid droplets of the suspension medium encompassed within a sheath comprising the first and second amphiphilic components, the active ingredient being contained in the liquid droplets, or in the sheath, or in both the liquid droplets and the sheath, wherein the first and second amphiphilic components and active ingredients are further selected such that, independently of the concentrations of the first and second amphiphilic components and the active ingredient, no solubilization of the vesicles in the suspension occurs.

Applicants claim, in independent claim 53, A non-invasive method of using a preparation in the form of vesicles suspended in a liquid suspension medium, the vesicles comprising a sheath of at least one layer of amphiphilic carrier substance, the amphiphilic carrier substance comprising at least two physiochemically different amphiphilic components, at least two of the components differing in their solubility in the liquid suspension medium by a factor of at least 10, the amphiphilic components selected such that independently of their concentration a solubilization of the vesicles does not occur. The method comprises applying the preparation to a permeation barrier and allowing the vesicles to transporting at least one active ingredient for medicinal or biological purposes into and through the permeation barrier.

Applicants' preparations offer a number of important advantages over currently available preparations because they are formulated such that each of the components may be added

without solubilization of the vesicles. Applicants unexpectedly found that for certain substance compositions, there is a saturation limit of one of the components in the membrane-like sheath of the vesicles and, as soon as this limit is reached, the addition of further amounts of this component will not lead to further incorporation of such molecules into the membrane. Rather, such addition will simply cause an increase in the free-floating of such molecules in the suspension medium. The vesicles remain stable and do not get solubilized. Further, Applicants preparations provide vesicles that, as driving pressure increases, permeability increases disproportionately or nonlinearly. In particular, applicants provide transfersomes, which differ from liposomes and from other carriers, with respect to several basic properties. Transfersomes are much larger than conventional micelle-like carrier formulations and are, therefore, subject to different diffusion laws. While the permeability of liposomes is a linear function of driving pressure, transfersomes exhibit permeability that increases disproportionately or nonlinearly as the pressure increases. This results in higher deformability characteristics of transfersomes. In order to stress the foregoing difference more clearly in the claims, the term "such that the permeation capability of the vesicles increases disproportionally or nonlinearly under increasing pressure" has been added to claims 22 and 53.

As set forth above, US'500 (and EP'160) clearly describes a method of forming a preparation and using a preparation wherein the vesicles specifically have a solubilization point. The edge active substances is selected and added in a concentration which amounts to up to 99 mol-% of the concentration required for the induction of droplet solubilization. Thus, methods of forming the preparation and using a preparation in accordance with US'500 specifically requires determining the conditions under which the edge active substances solubilize the vesicles and, based on this, adding the edge active substance in an amount that is up to 99 mol-% of the concentration required for solubilization. Thus, there is no explicit teaching in US'500 of applicants' claims. Rather, while the present claims are specifically directed to a method of producing and using a preparation wherein the vesicles have no solubilization point regardless of the amount of components added, US'500 is directed to a method of producing and using a preparation wherein the vesicles have a solubilization point based on the concentration of the edge active substance added, and edge active substance(s) are added in an amount below this concentration. Thus, US'500 teaches away from applicants' claims. Further, applicants claims

would not be inherent in US'500 because US'500 specifically teaches vesicles having a solubilization point and, thus, methods of using and producing a preparation in accordance with US'500 would necessarily lead to the production or use of vesicles having a solubilization point.

Regarding the Office's statement that applicant's arguments "are confusing and contradictory to their previous arguments" because "what is the point in adjusting the substance (more soluble component) content to less than 0.1% and argue that 'with US 500, if too much of a particular component is present in the preparation, the droplets will solubilize, thus, rendering the preparation ineffective'.", applicants' respectfully submit that the claims currently do not include adjusting the more soluble component content to less than 0.1%. Rather, the claims state that the first and second amphiphilic components and active ingredients are selected such that, independently of the concentrations of the first and second amphiphilic components and the active ingredient, no solubilization of the vesicles in the suspension occurs. Applicants prior argument, which the Office relies on, was directed to a prior claim 22 which contained two alternatives (1) an embodiment wherein there is no solubilization point (which is currently pursued in the pending claims) and (2) an embodiment wherein there is a solubilization point and the content of the more soluble component is adjusted to less than 0.1 mole percent of its content at which the enveloped droplets solubilize (which is not currently pursued in the pending claims and, thus, is irrelevant to the present claims). Thus, applicants' arguments are not contradictory to the previous arguments because they are directed to one of the alternative embodiments previously set forth in claim 22. The present claims do not set forth adjustment of the concentration of the more soluble component relative to the concentration at which the droplets will solubilize because the claims are directed to an embodiment wherein there is no solubilization point.

Accordingly, it is respectfully submitted that claims 22 and 53 are patentable over EP'160 (US'500). Claims 23-33, 49-52 and 53-92 depend from claims 22 and 53 and, likewise, are patentable over EP'160 (US'500). Reconsideration and withdrawal of the rejections is respectfully requested.

3. 35 U.S.C. 103 Rejections

Claims 22-33 and 49-92 are rejected under 35 USC 103(a) over EP 0 475 160 (English equivalent US 6,165,500 "US'500). Applicants respectfully traverse for the same reasons as set forth above regarding US'500.

As set forth above, US'500 (and EP'160) clearly describes a method of forming a preparation and using a preparation wherein the vesicles specifically have a solubilization point. US'500 does not expressly or inherently describe a method of producing or using a preparation such that the first and second amphiphilic components and active ingredients are selected such that, independently of the concentrations of the first and second amphiphilic components and the active ingredient, no solubilization of the vesicles in the suspension occurs.

Further, US'500 does not suggest applicants' method or forming or using the preparation in accordance with claims 22 or 53. Rather, US'500 specifically describes a method of forming a preparation and using a preparation wherein the vesicles specifically have a solubilization point. There is no teaching or suggestion that a preparation could even be formed wherein vesicles do not have a solubilization point. Rather, US'500 is based on a concept wherein the solubilization limit is approximated based on the concentration of at least one of the amphiphilic components and the concentration of that component is adjusted accordingly. Thus, there is no teaching or suggestion of applicants' claims nor is there any motivation to modify US'500 in accordance with applicants' teachings. Rather, this teaching comes purely from applicants' present disclosure.

Accordingly, it is respectfully submitted that claims 22 and 53 are patentable over EP'160 (US'500). Claims 23-33, 49-52 and 54-92 depend from claims 22 and 53 and, likewise, are patentable over EP'160 (US'500). Reconsideration and withdrawal of the rejections is respectfully requested.

CONCLUSION

It is believed the application is in condition for immediate allowance, which action is earnestly solicited. Should the Examiner wish to discuss any of the amendments and/or remarks made herein, the undersigned attorney would appreciate the opportunity to do so.

If for any reason a fee paid is inadequate or credit is owed for any excess fee paid, you are hereby authorized and requested to charge or credit Deposit Account No. 04-1105 under order no. 58069 (47126).

Respectfully submitted,

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